VERSION WITH MARKINGS TO SHOW CHANGES MADE
PURSUANT TO 37 C.F.R. §§1.121(c)

In the Claims:

Claim 25 has been amended as follows:

25. (Amended) A method according to claim 15, wherein the method further comprises selecting densified particles [using] by size classification.

Claim 26 has been amended as follows:

26. (Amended) A method according to claim 25, wherein the size classification of the densified particles is carried out [using] by sieving or cyclone separation.

Claim 40 has been amended as follows:

40. (Amended) A method of delivering a selected pharmaceutical agent to a vertebrate subject, said method comprising providing a compacted particulate pharmaceutical preparation according to claim 37, said preparation comprising the pharmaceutical agent, and delivering the preparation to a target tissue or cell of the vertebrate subject by needleless syringe.

Atty Dkt No. 7010-0001
USSN: 09/216,641
PATENT

REMARKS

Introductory Comments:

Claims 15-40 were examined in the Office Action dated 13 September 2001. Applicants note with appreciation that the Office has withdrawn the following rejections: **(a)** the rejection of claim 38 under 35 U.S.C. §102 over U.S. Patent No. 5,100,792 to Sanford; **(b)** the rejection of claims 15-37, 39 and 40 under 35 U.S.C. §112, first paragraph; and **(c)** the rejection of claims 24 and 40 under 35 U.S.C. §112, second paragraph.

However, claims 25 and 26 have now been objected to as informal. In addition, the following new claim rejections have been entered: **(1)** claims 15- 40 stand rejected under 35 U.S.C. §112, first paragraph, as nonenabled; **(2)** claims 15-30, 33-37 and 39-40 stand rejected under 35 U.S.C. §112, second paragraph as indefinite; **(3)** claims 15-20, 23-27, 29-31, 33-37 and 39-40 stand rejected under 35 U.S.C. §102(b) as unpatentable over U.S. Patent No. 5,630,796 to Bellhouse et al. ("Bellhouse1"); **(4)** claims 15, 28 and 38 stand rejected under 35 U.S.C. §102(b) as unpatentable over International Publication No. WO 94/23738 to McElligott et al. ("McElligott"); **(5)** claims 29, 30 and 32-39 stand rejected under 35 U.S.C. §102(e) as unpatentable U.S. Patent No. 6,010,478 to Bellhouse et al. ("Bellhouse2"); and **(6)** claims 15, 21 and 22 stand rejected under 35 U.S.C. §103(a) as unpatentable over Bellhouse1 in view of U.S. Patent No. 5,486,364 to King et al. ("King") and U.S. Patent No. 4,737,366 to Gergely et al. ("Gergely").

The objection to the claims and the new claim rejections are traversed for the following reasons.

Overview of the Amendment:

Claims 25 and 26 have been amended to correct the language informalities helpfully pointed out by the Office. More particularly, claims 25 and 26 have been amended to replace "using" with "by" as directed by the Office. Support for these amendments can be found in the claims as originally filed since "using" and "by" are typically employed interchangeably. In this regard, the undersigned has referred to a dictionary (Webster's New Collegiate Dictionary, 1977, G & C Merriam Co.) and found that "using" (the transitive verb) is defined as follows: "to carry out a purpose or action by means of," for example, to carry out a selection of particles (the purpose or action) by means of size classification. Accordingly no new matter has been entered by way of the amendments to claims 25 and 26, and the entry thereof is respectfully requested.

In addition, claim 40 has been amended to provide proper connection between the preamble and the body of the claim, again as helpfully pointed out by the Office. More particularly, claim 40 has been amended to more clearly recite that the pharmaceutical preparation contains the pharmaceutical agent that is to be delivered. Support for this amendment can be found in the claim as originally filed, and throughout the specification. Accordingly no new matter has been entered by way of the amendment to claim 40, and the entry thereof is respectfully requested.

Attached herein above are marked-up versions of the changes made to the claims by the current amendment. The attached pages are captioned "Version With Markings to Show Changes Made."

The Objection to the Claims:

Claims 25 and 26 were objected to as informal on the basis "that the term 'using' is not grammatically correct." The Office has indicated that the term "by" should be used instead of "using," and appropriate correction was required.

In response, applicants draw the Office's attention to the amendments to claims 25 and 26 submitted herewith, whereby applicants have made the requested language changes. Reconsideration and withdrawal of the objection to claims 25 and 26 is thus respectfully requested.

The Rejections Under 35 U.S.C. §112, first paragraph:

Claims 15-40 stand rejected under 35 U.S.C. §112, first paragraph, as nonenabled. This new Section 112 rejection is more or less co-extensive with the previous rejection (the rejection of claims 15-37, 39 and 40 as tendered in the Office Action dated 26 December 2000), and seems to be wholly premised upon the combination of a new interpretation of the specification being proposed by the Office and a generic rejection for genetic pharmaceuticals, wherein the basis for the rejection appears to be a preconceived notion of strict nonenablement for such compositions.

More particularly, the Office acknowledges that the specification is enabling for "a method for forming densified particles from a particulate pharmaceutical preparation containing a peptide or a protein, comprising pressing or grinding said pharamcaeutical preparation to provide a compacted pharmaceutical preparation and size-reducing the compacted preparation onto densified particles ...; the same densified or compacted particulate pharmaceutical composition and a unit dosage container for a needleless syringe comprising the same; and a method for transdermally delivering the same." Office Action at

pages 2-3, bridging paragraph. Applicants are in agreement with the Office with respect to the above passage, and note that the Office has not questioned the enablement of the claims as they relate to these embodiments in the present rejection.

However, the Office then asserts that the specification is enabling for "a method for forming densified particles from a particulate pharmaceutical preparation containing a gene construct, wherein the step of forming densified particles is the step of coating onto biolistic core carriers or encapsulating a gene construct in a microparticle for transdermal delivery thereof by needleless injection." Office Action at page 3, second paragraph. The Office then asserts that the above gene construct-specific disclosure is not enabling for other embodiments of the claims, and concludes "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claims." Applicants respectfully disagree.

The above-noted interpretation of applicants' disclosure regarding methods for producing densified pharmaceuticals containing a gene construct is dead wrong. Applicants draw the Office's attention to the following parts of the specification: page 8, lines 11-25 wherein it is stated "[t]he present invention is based on the surprising discovery that substantially solid particles of nucleic acid molecules can be delivered into cells of mammalian tissue *without the need for biolistic core carriers*," (emphasis added); page 9, lines 9-28 wherein it is stated "the nucleic acids to be delivered can be converted from non-dense pharamceutical powders or particulate formulations (e.g.,those having particle densities below that required for transdermal delivery from a needleless syringe) into densified (compacted) particles .... [i]n a substantial departure from conventional particle bombardment techniques the nucleic acid particles transferred using the method of the

present invention *are not delivered using biolistic core carriers*," (emphasis added); and page 21, lines 8-15, wherein it is again clearly stated that "the present invention allows for the highly efficient delivery of solid particles of nucleic acid molecules ... the method utilizes biolistic gene transfer techniques *yet surprisingly allows for the delivery of nucleic acid molecules without the need for biolistic core carriers*" (emphasis added).

Accordingly, contrary to the Office's assertion, applicants' specification has nothing whatsoever to do with using biolistic core carriers, rather applicants distinguish over this prior methodology throughout the specification and provide the claimed methods as a distinct alternative to the use of biolistic core carriers.

With regard to the Office's second assertion regarding encapsulating a gene construct into a microparticle as a method for forming densified nucleic acid preparations, applicants cannot find any basis for this interpretation of the specification. Applicants do disclose methods for forming densified nucleic acid particles, where a nucleic acid composition is compacted and then size-reduced (e.g., ground) to form suitable particles. Applicants draw the Office's attention to the specification at page 28, line 12 through page 32, line 16 wherein detailed disclosure is provided regarding the claimed methods. Obviously, microencapsulation has nothing to do with the claimed methods that expressly include a compaction step to provide the condensed (densified) powders. Disclosure regarding what is meant by compaction is provided throughout the specification, see, e.g., page 9, lines 9-17; page 11, line 4 through page 12, line 17; page 29, line 28 through page 30, line 5; page 31, line 14 through page 32, line 16. As can be seen these passages, the critical feature is that compaction of typically porous starting materials results in a reduction of porosity and a corresponding increase in the bulk density of the densified material. Microencapsulation has no overlap with this methodology.

Accordingly, it is respectfully submitted that the Office's interpretation of the specification and claims as disclosing and enabling coated biolistic carrier particles or encapsulated microparticles is improper and not supported by any fair reading of applicants's submission.

With regard to the generic issues raised regarding genetic pharmaceuticals, applicants respectfully traverse as follows. The Office has asserted that it would require undue experimentation to make and use the invention as broadly claimed on the basis that "the instant specification fails to teach any other forms [i.e., forms other than compaction under pressure] of compacting the particulate pharmaceutical preparations." Office Action at page 5, third paragraph. Applicants respectfully fail to understand the basis for this rejection. Each and every one of applicants' claims expressly recites a compaction (densification) limitation, and applicants have demonstrated these methods over and over throughout the specification, using disparate molecules (some nucleic acids, some biopharmaceuticals) and have even provided working examples. Accordingly, applicants submit that they have indeed provided sufficient disclosure to enable the skilled artisan to make and use the claimed invention, and that there would not be a necessity for undue experimentation.

The Office has asserted that "it is unclear whether the gene construct in the densified pharmaceutical preparation of the present invention is still intact and that it is not susceptible to nicks or degradation due to the compacting process under high pressure ... such that the pharmaceutical preparation has any beneficial use." Office Action at page 6, first paragraph. The Office specifically cites the lack of hGH expression seen in Example 2 in support of its assertion. Applicants strongly object to this assertion. What the Office seems to have completely ignored is the fact that applicants have demonstrated the "beneficial

utility" of their densified nucleic acid preparations many times over in the working examples. In Example 1, a densified gene construct encoding the β-galactosidase marker was delivered into cells. As can be seen by the results, cells transfected with the densified nucleic acid preparations were blue-stained after contact with X-Gal, demonstrating that the β-galactosidase marker both was expressed and functional. In Example 2, a densified gene construct encoding the Green Fluorescent Protein (GFP) marker was delivered into living animals. Histology was carried out, and the tissue was exposed to UV radiation. GFP activity was seen, demonstrating that the GFP gene construct was both expressed and fully functional. In Example 2, a subsequent study was carried out with the β-galactosidase marker gene in living animals, and once again β-galactosidase activity was shown, demonstrating both expression and function of the gene product. Finally, in Example 2, a densified gene construct encoding hGH was administered. This was administered at a very small dose (0.1 μg) which was a full order of magnitude less than the β-galactosidase marker (1 μg). As applicants noted in the example, the lack of expression was not due to some denaturation event, rather it was due to too small of a dose having been administered.

The Office has objected that applicants have not demonstrated how to make and use the claimed invention on the basis that "at the filing date of the present application, gene therapy was considered to be immature and unpredictable" (Office Action at page 6, second paragraph), "there is no correlation between the expression of GFP or β-galactosidase with the desired therapeutic results for treating a plethora of diseases" (Office Action at page 7, and "there is no evidence of record that the densified pharmaceutical composition comprising a gene construct could provide any expression of a relevant therapeutic gene product *in vivo* at any level via a needleless injection" (Office Action at page 7). The Office supports these assertions by reference to Palmer et al. (1991) *Proc.*

Natl. Acad. Sci. 88:1330-1334 (cited for the proposition that "it is well known that transgene expression *in vivo* is very transient [since] expression of human factor IX ... was transient and vanished 1-5 weeks post-transplantation") and Riddell et al. (1996) *Nature Med.* 2:216-223 (cited for the proposition that HIV patients developed CTL responses to transduced T cells). Applicants respectfully submit that these assertions are either incorrect or inappropriately applied against applicants' claims.

Initially, in response to the Office's assertion that applicants' marker gene expression (e.g., GFP or β-galactosidase) has "no correlation with desired therapeutic effects" and "there is no evidence of record that [applicants' compositions] could provide any expression of a relevant therapeutic gene product *in vivo* at any level via a needleless injection, let alone a therapeutic expression level" is scientifically incorrect. The entire industry uses marker gene expression as a direct correlate to therapeutic gene expression. This is simply how research is carried out in the industry. An assertion that the use of marker genes provides no information whatsoever is simply incorrect. What the instant rejection implies is that the Office will accept nothing more than actual clinical trial information as evidence of enablement of a straight-forward method of compacting (densifying) compositions that contain a nucleic acid molecule. Applicants are unaware of any statutory or other legal basis for this sort of requirement. In fact, the Office's apparent requirement that applicant must have actually carried out multiple clinical studies for all conceivable compositions that could meet the claims is improper. This is because if such a requirement was actually valid, it would discourage inventors from disclosing and teaching their discoveries for the public's benefit until an exhaustive experimental study into any and all possible embodiments had been completed, which discouragement is antithetical and in direct contradiction of the guiding principals underlying Section 112. See, e.g., *Rohm &*

Hass Co. v. Dawson Chemical Co., 217 USPQ 515, 563-564 (S.D. Tex. 1983), *rev'd on other grounds*, 220 USPQ 289 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Applicants submit that their only obligation under Section 112 is to provide a specification that enables one skilled in the art to make and use the invention as claimed. Claims 15-28 recite methods for forming densified particles from a particulate pharmaceutical preparation, wherein the densified particles are suitable for transdermal delivery using needleless injection. Applicants have enabled how to carry out these methods. Claims 29-37 recite densified particulate pharmaceutical compositions. Claim 38 recites particles of a suitable size and density for transdermal delivery by needleless injection consisting of a gene construct and an excipient. Applicants have enabled how to make and use these particles. Claim 39 recites a unit-dosage container for a needleless syringe that contains a compacted particulate pharmaceutical prepared using the methods of the present invention. Applicants have enabled how to make and use such containers. Claim 40 recites a method for delivering a compacted pharmaceutical prepared using the methods of the present invention, wherein the preparation is delivered to a cell or tissue using a needleless syringe. Applicants have clearly enabled how to carry out the recited method. With regard to the Office's assertion that other delivery routes could be encompassed and the claims are thus nonenabled, applicants remind the Office that if applicants' specification contains within it a connotation of how to use the invention, and the art recognizes that standard modes of administration are known and contemplated (e.g., needleless injection techniques), then 35 U.S.C. §112, first paragraph, is satisfied. See *In re Johnson*, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 144 USPQ 637,643 (CCPA 1965); and see also *In re Brana*, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).

With regard to the Office's reliance upon the Palmer reference to show nonenablement, (that it is well known that transgene expression *in vivo* is very transient since expression of human factor IX was transient and vanished 1-5 weeks post-transplantation), applicants respectfully question how this issue could have any relation to enablement of applicants' claims. Is it the Office's position that the hemophiliac obtaining a Factor IX gene construct that provides 1-5 weeks of functional Factor IX would think that gene technology does not work? Applicants suggest that this is simply not the case, the transferred gene clearly worked, it even worked for a period of between 1 week and over a month. With regard to the Office's reliance upon the Riddell reference to show nonenablement, applicants respectfully are at a loss to see the relevance of this reference to their claimed invention. Clarification of this issue is respectfully requested should the Office maintain the instant ground of rejection.

Finally, the Office has asserted that nucleic acid immunization is so unpredictable that this renders applicants' methods that could include densifying compositions containing nucleic acid molecules nonenabled. Office Action at page 8, second paragraph. Applicants respectfully disagree. Nucleic acid immunization has been carried out for over a decade now, with multiple preclinical and clinical trials demonstrating time and again that delivered gene constructs are both expressed and provide a meaningful immune response in all sorts of animal models and in man.

Applicants have provided sufficient guidance to the skilled artisan with respect to how to make and use applicants' claims, and are thus in full compliance with Section 112. The Office's assertion that the claims are not enabled is simply not supported by any fair reading of applicants' detailed description of the invention, particularly when read in light of the numerous working examples provided therein. For all of the foregoing reasons, then, the

rejection of claims 15-40 under 35 U.S.C. §112, first paragraph, is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

The Rejections Under 35 U.S.C. §112, second paragraph:

Claims 15-30, 33,37 and 39-40 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite. In particular, the Office had objected that "it is unclear what is encompassed by the phrase 'compacting the preparation'" and has concluded that "the metes and bounds of the claims can not be clearly determined." Clarification has been requested.

In response, applicants direct the Office's attention to the specification at page 35, lines 18-22 wherein it is clearly stated that "compaction of porous pharmaceutical compositions will generally result in a reduction in porosity, and a concomitant increase in bulk (envelope) density." The idea of compacting preparations as recited throughout applicants' claims can be found time and again throughout applicants' specification. The Office's attention is drawn to the specification at, *inter alia*, page 9, lines 9-17; page 11, lines 4-34; page 12, lines 1-17; and page 30 line 1 through page 32, line 16. These portions of the specification, as well as the working examples, provide ample guidance for what is meant by "compacting the preparation." Numerous tests are disclosed guiding the skilled artisan to ascertain if there has been a desired densification. Accordingly, applicants submit that they have indeed provided sufficient clarity. Reconsideration and withdrawal of the rejection of claims 15-30, 33,37 and 39-40 under 35 U.S.C. §112, second paragraph, is thus respectfully requested.

Claims 15-26, 29-30, 33-37 and 39-40 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite. In particular, the Office has objected that "it is unclear

what is encompassed by the phrase 'pharmaceutical preparation', and therefore it renders the claims indefinite. Applicants respectfully disagree.

Applicants note that the primary purpose of Section 112's requirement for clarity and precision is to ensure that the public is informed of the metes and bounds of the claimed invention. Applicants also note that definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the disclosure provided by the specification; (2) the teachings of the prior art; and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Applicants respectfully submit the term "preparation" is a commonly employed term in the pharmaceutical arts. In fact, the undersigned has referred to a common dictionary (Webster's New Collegiate Dictionary, 1977, G & C Merriam Co.) and found the following under the definition for preparation: "a medicinal substance made ready for use." Referring to applicants' specification, numerous medicinal substances are disclosed, where these substances are rendered into a compacted (densified) particulate form and thus made ready for use in applicants' recited methods for needleless injection. Accordingly, if one views the claims using both the common English definition of "preparation" and the definition as would be given by one or ordinary skill in the art, the metes and bounds of the claimed invention are clearly delineated. Accordingly, the rejection of claims 15-26, 29-30, 33-37 and 39-40 under 35 U.S.C. §112, second paragraph, is improper. Reconsideration and withdrawal of the rejection is respectfully requested.

The Rejections Under 35 U.S.C. §102:

Claims 15-20, 23-27, 29-31, 33-37 and 39-40 stand rejected under 35 U.S.C. §102(b) as unpatentable over Bellhouse1. In particular, the Office asserts that "Bellhouse1

teaches "a method for preparing as well as delivering transdermally into a mammalian subject particles of a powdered therapeutic agent .... that is ground (a form of compacting the powdered therapeutic agent with a pestle and mortar as shown in example 1 of the instant specification) and sieved to a precise diameter." In other words, the Office has equated the grinding that Bellhouse1 carried out to comminute pharmaceuticals into small particles with applicants' recited compaction methods. Applicants respectfully traverse.

The Office has recited the passage from Bellhouse1 (column 4, lines 13-14) as disclosing applicants' compaction methods. This is incorrect. "Grinding," as that term is used in Bellhouse1, is clearly used as a way to comminute a powder into smaller particles, not to increase density. The fact that Bellhouse's grinding has no effect whatsoever on the resultant density of the smaller particles is clear if the rest of the recited passage is read, particularly the material at column 4, lines 19-22 where Bellhouse et al. state "*a substantially inert carrier may have to be included* to provide the particles with the required size and *mass* for adequate penetration, *particularly if the therapeutic agent is potent or of low density*." If, as the Office has suggested, Bellhouse1's grinding was suitable for increasing the density of the smaller particles, why would Bellhouse et al. then teach that carriers must be used to increase mass of agents having low density? Applicants submit that the only rationale answer is because the grinding had no effect on the density of their powders.

Applicants likewise disclose throughout their specification that grinding is used to size reduce a compacted material, see, e.g., page 33, lines 12-15 ("when spray-dried and lyophilized pharmaceutical particles are ground or milled, they yield very small, light and non-dense particles that are poorly suited for delivery through skin or mucosal tissues"); page 11, lines 18-23 ("the resulting compacted material is then size-reduced using

conventional methods"); page 12, lines 6-11 ("the densified material can then be reground"); page 31, lines 20-22 ("the resulting compacted material is then coarsely reground until visually broken up"); and page 34, lines 10-12 ("the resulting compacted material is then coarsely reground until visually broken up").

Accordingly, the Office's assertion that Bellhouse's grinding "is a form of compacting the powdered therapeutic agent" is an incorrect reading of Bellhouse1. Contrary to the Office's assertions, the pharmaceutical powders disclosed by Bellhouse1 do not have the same characteristics as applicants' recited compacted compositions. Since anticipation of a claim under §102 *requires* that each and every element of the claims be inherent in, or disclosed expressly by the anticipating reference (*Constant v. Advanced Micro-Devices, Inc.*, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988)), Bellhouse1 cannot anticipate applicants' claims. Reconsideration and withdrawal of the rejection of claims 15-20, 23-27, 29-31, 33-37 and 39-40 under 35 U.S.C. §102(b) is thus respectfully requested.

Claims 15, 28 and 38 stand rejected under 35 U.S.C. §102(b) as unpatentable over McElligott. In particular, the Office asserts "McElligott et al. disclose the preparation of a microparticle composition for the controlled release of a nucleic acid ... by interacting with the promoting material and a biocompatible polymeric matrix, the nucleic acid preparation is compacted with respect to free nucleic acid molecules." The Office then concludes "therefore, McElligott et al. anticipate the instant claims." Applicants respectfully disagree.

Claim 15 recites a method for forming **(a)** densified particles using **(b)** a compacting step to provide a compacted preparation and then **(c)** a size reducing step to produce particle of a certain size. Claim 28 depends from claim 15, and thus includes all of these

same base limitations. Accordingly, in order for McElligott to anticipate, each and every element of the claims including elements (a), (b) and (c) must be inherent in, or disclosed expressly by McElligott. This requirement is clearly not met. McElligott does not teach or disclose a method for densifying particles. The Office's assertion that encapsulated nucleic acid particles are compacted has no relevance to an increase in density of the preparation. McElligott also does not teach or suggest a compacting step, nor a subsequent size reducing step. Since exclusion of a single claimed element from a prior art reference is enough to negate anticipation by that reference (*Atlas Powder Co. v E.I. du Pont De Nemours & Co.* 224 USPQ 409, 411 (Fed. Cir. 1984)), and McElligott excludes not one but three claimed elements, this reference simply cannot anticipate applicants' claims.

Claim 38 recites particles of a suitable size and density for transdermal delivery by needleless injection. Since McElligott is completely unrelated to transdermal delivery, the Office must be proceeding under a theory of inherency, that is, the Office must be asserting that McElligott microparticles are inherently suitable for transdermal delivery using a needleless injector. Applicants respectfully disagree. Section 2112 of the M.P.E.P. expressly cautions that "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic," (citing *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)), and instructs that "in relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art" (citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)). The Office has not even come close to establishing that the McElligott microparticles would necessarily have this critical feature, and this reference simply cannot anticipate applicants' claim.

For all fo the foregoing reasons, then, the rejection of claims 15, 28 and 38 under 35 U.S.C. §102(b) is improper. Reconsideration and withdrawal is thus respectfully requested.

Claims 29, 30 and 32-39 stand rejected under 35 U.S.C. §102(e) as unpatentable over Bellhouse2. The Office asserts that Bellhouse2 discloses delivery of RNA or DNA into skin using a needleless syringe. The basis for this rejection must either be that applicants are not entitled to their priority claims, or that the proper 102(e) date for the Bellhouse2 disclosure of delivering nucleic acids extends back to the PCT filing date where the US was designated. Neither of these are correct, and applicants thus respectfully traverse the rejection.

More particularly, Bellhouse2 was filed on 14 August 1997 as a continuation-in-part of PCT/GB96/00340. All of the disclosure regarding nucleic acids was added to the C-I-P at this time, making the effective 102(e) date for the nucleic acid-specific subject matter 14 August 1997. Applicants have claimed priority to their 11 September 1996 foreign filing, wherein they first disclosed delivery of densified nucleic acids. Accordingly Bellhouse2 is not available as 102(e) art, and the rejection is improper. Reconsideration and withdrawal of the rejection of claims 29, 30 and 32-39 under 35 U.S.C. §102(e) is thus respectfully requested.

The Rejection under 35 U.S.C. §103:

Claims 15, 21 and 22 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Bellhouse1 in view of King and Gergely. More particularly, the Office asserts that Bellhouse teaches that a powder is ground ("a form of compacting the powdered therapeutic") and then delivered using transdermal needleless

injection. King and Gergely are cited as showing tablet compression methodologies without heat or shear. The Office then concludes that the claims are obvious over this combination. Applicants respectfully disagree.

Section 2143 of the M.P.E.P. sets forth the following three basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine the references; (2) there must be a reasonable expectation of success for the modification and/or combination; and (3) the prior art reference must teach or suggest all the claim limitations. When assessing these issues, (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight; and (4) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicant submits that the Office has failed to satisfy these criteria, and has thus failed to establish *prima facie* obviousness over its asserted combination.

As discussed herein above, it is clear that the primary reference (Bellhouse1) fails to teach or even so much as hint or suggest a method for forming densified particles. The "grinding" that the Office has seized upon is clearly used by Bellhouse et al. as a way to comminute a powder into smaller particles, not to increase density. It is also clear that not a single one of the cited secondary references teaches or even so much as suggests such methods. Both of the secondary references relate wholly to forming tablets. Accordingly, the cited prior art references do not teach or suggest applicants' recited limitations, and the Office has failed to make its *prima facie* showing of obviousness.

For these reasons, then, the rejection of claims 15, 21 and 22 under 35 U.S.C. §103(a) is improper. Reconsideration and withdrawal is thus respectfully requested.

Atty Dkt No. 7010-0001
USSN: 09/216,641
PATENT

CONCLUSION

Applicants submit that the claims define an invention which is both novel and nonobvious over the prior art. Accordingly, a Notice of Allowance is believed in order and the issuance of such a notice is respectfully requested. Applicants further ask that, should the Examiner note any minor remaining issues that may be resolved with a telephone call, that he contact the undersigned in the UK at +44 1865 332 600.

Respectfully submitted,

Date: 13 March 2002

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